Journal of Surgical Oncology 1997;65:76–81

Results of Preoperative Intraluminal Brachytherapy Combined With Radical Surgery for Middle and Lower Rectal Carcinomas

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Background: Radiation therapy in the treatment of rectal carcinoma has received attention. We attempted to learn whether preoperative intraluminal brachytherapy (IBT) gives an advantage in local control and/or prolongation of survival.
Methods: One hundred and fifteen patients with middle and lower rectal carcinoma with penetration into or through the rectal wall were consecutively treated with preoperative IBT and radical operation. Patients were divided into the moderate-dose group (group A: 16–40 Gy; n = 96) and the high-dose group (group B: 40–80 Gy; n = 19). A control group of 115 rectal carcinoma patients who received no radiation prior to radical surgery was compared (group C).
Results: The rate of sphincter-saving resection was 72% in group A, 63% in group B, and 42% in group C (group A vs. group C; $P < 0.0001$). The local recurrence rate at 5 years was 11% in group A, 6% in group B, and 26% in group C (group A vs. group C; $P = 0.005$). The 5-year survival rate was similar among the three groups.
Conclusions: These results suggested that IBT contributed to the improvement of local control but not survival after radical resection of rectal carcinomas. The application of IBT might be useful in preserving the intestinal continuity for rectal carcinomas.
J. Surg. Oncol. 1997;65:76–81.

KEY WORDS: **rectal carcinoma; radiation; surgery; intraluminal brachytherapy**

INTRODUCTION

A variety of options for various conditions of rectal tumors are necessary for optimal oncologic results and postoperative quality of life. Of crucial importance in the surgical procedure is the avoidance of permanent stoma. However, oncologic results in rectal surgery have not improved, despite recent advances such as new operative techniques and devices [1]. Surgeons have sought an effective conventional adjuvant therapy to use with the operations for rectal tumors, especially sphincter-saving resection (SSR).

In the last few decades, radiation therapy in the treatment of rectal carcinoma has received attention. External beam radiation has been used as an adjuvant therapy to potentially curative surgery [1,2]. Endocavitary irradiation delivering a high dose of radiation directly to rectal tumors with limited penetration was introduced with significant success by Papillon [3,4]. In addition to the remote afterloading technique, intraluminal brachytherapy (IBT) has become widely available [5]. Since 1986 we have used preoperative IBT combined with surgery for

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Accepted 3 March 1997

TABLE I. Clinical Characteristics of the Patients With Rectal Carcinoma

	Group A (n = 96)[a]	Group B (n = 19)[b]	Group C (n = 115)[c]	*P* value[d]
Age (y/o); median value (range)	59 (25–87)	65 (46–86)	59 (30–83)	
Sex (male/female)	69/27	10/9	75/40	
Tumor height (cm); median value (range)	5* (2–11)	4 (1–9)	5.5* (2.5–12.5)	*0.02
Dukes' classification				
A	32	7	31	
B	16§	3	32§	§0.009
C	41	5	44	
D	7	4	8	
Histological differentiation				
Well	44§§	16	76§§	§§0.003
Moderate	44†	2	31†	†0.004
Poorly	6		2	
Mucinous	2	1	5	
Others			1	
Operation				
Low anterior resection	12		22	
Anoabdominal rectal resection and coloanal anastomosis	57‡	12	26‡	‡0.000
Abdominoperineal rectal excision	24¶	7	58¶	¶0.000
Total pelvic exenteration	2		6	
Hartmann's procedure	1		3	
Median follow-up months (range)	49.5 (8.6–60)	60 (6–60)	47.5 (9.2–60)	

[a]Moderate-dose group.
[b]High-dose group.
[c]No radiation group.
[d]Superscript symbols (*, †, ‡, §, §§, ¶) indicate values compared to achieve *P* value.

rectal carcinoma. The purpose of the present report was to review the experience of our institution with all patients treated by IBT combined with radical surgery for rectal carcinoma. We attempted to learn whether or not IBT gave an advantage in local control and/or prolongation of survival.

PATIENTS AND METHODS

Patients

Between October 1986 and October 1995, 115 patients with middle or lower rectal cancer were treated with preoperative IBT combined with radical surgery after giving informed consent. All tumors were diagnosed as being stage T2 according to the TNM staging system [6] by preoperative examination using endoscopy, contrast enema study, transrectal ultrasonography, computed tomography, or magnetic resonance imaging [7]. The patient profile is shown in Table I. The patients were divided into two groups, according to IBT dose; group A (n = 96) received a moderate dose (16–40 Gy) and group B (n = 19) received a high dose (40–80 Gy). Another 115 patients comprised the controls who received no radiation (group C): 62 patients who underwent surgery for rectal carcinomas between 1978 and 1986 without any preoperative adjuvant therapy (before the introduction of IBT) and 53 patients who, under informed consent, did not select IBT. All of the 230 patients' records were reviewed by our staff.

Preoperative IBT Technique

All of the patients were treated with a remote afterloader RAL-30A and RAL-40A (Toshiba, Tokyo, Japan). An insertion tube consisting of inner and outer tubes was directly attached to the afterloading machine. To protect perianal skin a hip shell, made of thermal plastic resin ensuring fixation of the tubes during the radiation treatment, was constructed for each patient. The patients were placed in the left-lateral position. The outer tube was fixed to the hip shell and inserted into the rectum. The inner tube was then inserted into the outer tube, and the irradiation source was applied. The irradiation source was Cobalt-60 with an activity of 1.7 or 2.6 Ci. Single doses ranged from 4 to 40 Gy, with total doses from 16 to 80 Gy. The irradiation source was moved slightly over the length of the tumor at 1 cm intervals. The operation was performed 2 weeks after radiation therapy.

Operation

The operations were classified into two categories, SSR and rectal amputation. SSR was performed in 81 of the 115 cases (70.4%) comprising groups A and B (Fig. 1). These SSRs consisted of 12 low anterior resections for tumors located at the upper and middle rectum and 69 anoabdominal rectal resections and coloanal anastomoses for tumors located at the lower rectum. Rectal amputation was performed as abdominoperineal rectal ex-

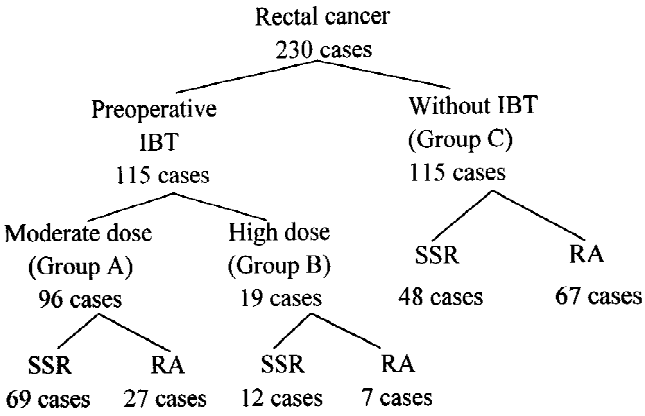

Fig. 1. A treatment tree of rectal carcinoma. Group A includes the patients treated with a moderate dose (16–40 Gy) of preoperative intraluminal brachytherapy (IBT); group B includes the patients treated with a high dose (40–80 Gy) of preoperative IBT; all the patients in group C were treated without radiation. SSR, sphincter-saving resection; RA, rectal amputation with permanent stoma (including Hartmann's procedure).

Fig. 2. A photomicrograph of lower rectal cancer which indicated total regression (black arrowheads) of preoperative IBT in resected specimens. Internal sphincteric muscles are indicated by a black arrow. (H.E. staining; ×20).

cision (APE) in 31 cases, total pelvic exenteration in 2 cases, and Hartmann's procedure in 1 case. APE was performed for cancers penetrating the rectal wall. It was also used when there was an inadequate surgical margin to perform an SSR. Total pelvic exenteration was used for tumors invading adjacent organs.

Pathological Examination

Surgical specimens were fixed by formalin and embedded in paraffin for hematoxylin-eosin staining. All tumors were classified according to Dukes' modification after the operation [8]. The sections were selected from the area including the maximum diameter of each tumor along the longitudinal axis or the healed area in the case of a grossly ablated tumor. The examined sections of each tumor were those median and bilateral sections at intervals of 5 mm. The invasion depth of irradiated tumors was defined by the deepest infiltrating tumor cells which were recognized as viable in the resected specimen. Histopathologic grading was defined from the resected specimen. If tumor cells were not seen in the pathologic slides, the histologic diagnosis was based on the preoperative biopsy specimen. We classified totally ablated tumors without lymph node involvement as Dukes' A, and those with nodal involvement as Dukes' C.

A quantitative morphologic measurement of the radiation effect was made of each specimen to determine the proportion of tumor nest to background stroma, using the image analyzing system (IBAS-20, Zeis, Germany) [9].

Clinical Assessment

The clinical check points were 1) radiation effect, 2) local and distant recurrence, and 3) death from cancer. Follow-up information was obtained from office charts, hospital records, and telephone interviews. No patients were lost to follow-up. Median follow-up was 54 months after the initial operation. Probability curves for local recurrence and survival were generated by the Kaplan-Meier product-limit method. The significance of these curves was compared using a log-rank test including a Bonferroni adjustment. The characteristics of patients and complications were assessed using a chi-square test. Significance was assigned to P values < 0.05.

RESULTS

There were no hospital deaths among the 115 patients who were treated with preoperative IBT.

Pathologic Examination

Various degrees of radiation effect were seen in all radiated tumors. Morphologic changes under microscopic examination were shown in all tumors and characterized as follows: the appearance of giant cells with atypical nuclei, nuclear karyorrhexis, coagulation necrosis of the tumor and acellular mucin lakes, and transmural radiation fibrosis (Figs. 2, 3). Total tumor regression was observed in 12 cases (10 cases in group A and 2 cases in group B).

The precise analysis of resected specimens indicated a direct effect of IBT on rectal carcinoma, as shown in Figure 4. The proportion of residual tumor nest to background stroma was identified as median values, 17% in group A, 17% in group B, and 82% in group C. The diameter, height, and proportion of residual nest of the tumor in group A did not differ from that in group B; however, these three values were significantly lower than those of group C.

The median number of regional lymph nodes collected

Fig. 3. A photomicrograph of the radiation effect in a regional lymph node. Morphological changes, nuclear karyorrhexis, coagulation necrosis of the tumor, and acellular mucin lakes, are shown (black arrows). (H.E. staining; ×33).

from each tumor was 14 (range from 4 to 45) in the resected specimen. The numbers of positive nodes in the Dukes' C cases were median 4, range 1–11 in group A; median 5, range 2–8 in group B; and median 5, range 1–11 in group C. There was no significant difference among the three groups in this parameter. As for the distribution of lymph node metastasis in the Dukes' C patients, lymph node metastases localized in perirectal tissue were seen in 30 of the 41 Dukes' C patients in group A, in 2 of the 5 in group B, and in 15 of 44 patients in group C. There was a significant difference (df = 1, $\chi^2 = 14.1$, $P = 0.02$) between group A and group C. We showed a representative pattern of total tumor regression in the lymph nodes in group A (Fig. 3). These results suggest that IBT had the direct effect of decreasing cancer cells in not only the tumor, but also in adjacent lymph nodes.

Complications

Group B had IBT-related complications such as radiation ileitis and perianal skin troubles; 14 of the 19 patients had complications, significantly more (df = 1, $\chi^2 = 8.45$, $P = 0.04$) than group A (36 of the 96 patients). Surgical interventions for complications were required in 7 of the 19 patients in group B and in 7 of the 96 in group A. The difference between groups A and B was statistically significant (df = 1, $\chi^2 = 8.91$, $P = 0.027$). Three of 19 patients in group B were obliged to convert to permanent stoma after initial SSR due to complications. The functional results in group B after coloanal anastomosis were also significantly poorer than those in group A. Many of the patients in group B suffered from high-frequency stooling and soiling in the early postoperative period and urgency and incomplete evacuation in the late phase [10].

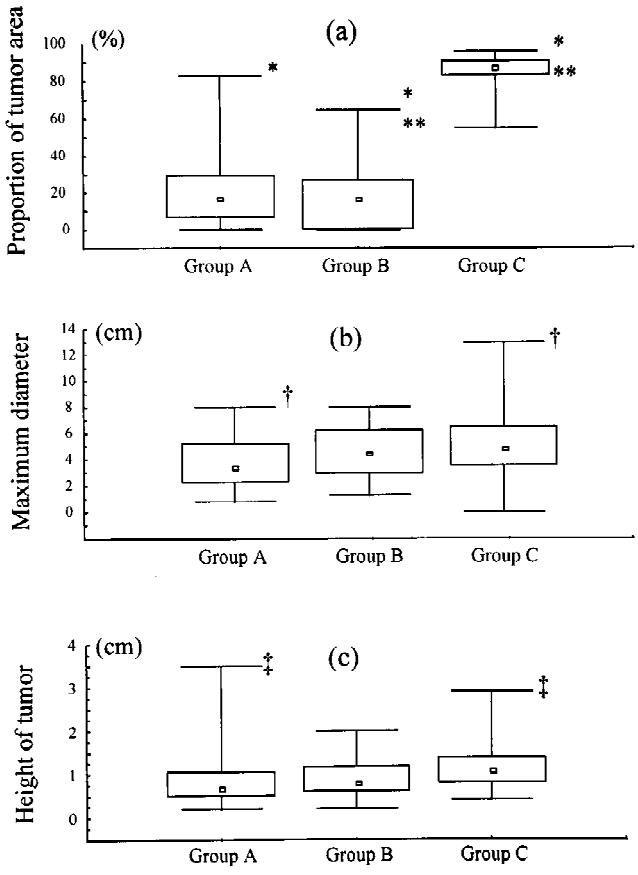

Fig. 4. The distribution of **(a):** proportion of residual tumor nest to background stroma; **(b):** tumor diameter; and **(c):** height in the three groups. Significant differences between the groups: * $P < 0.001$, ** $P < 0.001$, † $P = 0.001$, ‡ $P < 0.001$.

TABLE II. Pattern of Failure of the Patients With Rectal Carcinoma After Operation

	Group A (n = 96)[a]	Group B (n = 19)[b]	Group C (n = 115)[c]
Local only	2	1	11
Local + distant	6	0	13
Distant only	16	3	8
Disease-free survivors	69	13	75

[a]Moderate-dose group.
[b]High-dose group.
[c]No radiation group.

Recurrence and Survival

The sites of tumor recurrence are listed in Table II. Local recurrence was seen in 8 patients in group A, 1 patient in group B, and 24 patients in group C. Distant recurrence was seen in 22 patients in group A, 3 patients in group B, and 19 patients in group C. The number of disease-free surviving patients in each group was 69 patients (72%) in group A, 13 (68%) in group B, and 75 (65%) in group C. The cumulative local recurrence curve of each group is shown in Figure 5. The actuarial prob-

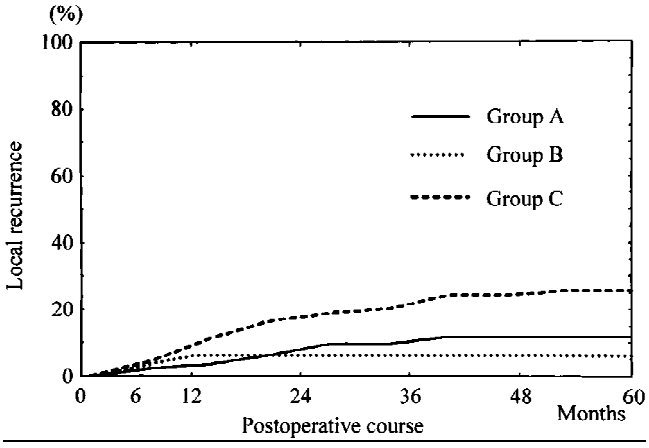

Fig. 5. Cumulative local recurrence curve in the three groups. Significant differences between groups A and C: $P = 0.005$.

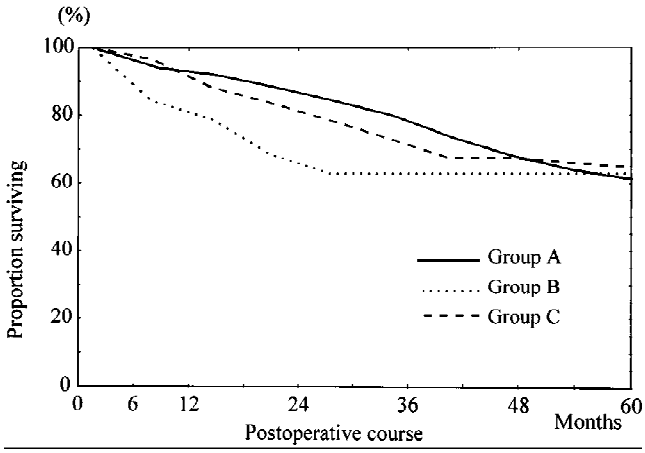

Fig. 6. Cumulative survival curve of the three groups. There were no significant differences among the groups.

ability of local recurrence at 5 years was 11% in group A and 26% in group C. The actual local recurrence rate was 6% in group B. There was a significant difference between groups A and C in overall local failures ($P = 0.005$). The local recurrence rates by tumor stage for group A were: Dukes' A, 0 of 32 (0%); Dukes' B, 1 of 16 (6%); Dukes' C, 7 of 41 (17%); Dukes' D, 0 of 7 (0%); for group B: Dukes' A, 0 of 7 (0%); Dukes' B, 0 of 3 (0%); Dukes' C, 1 of 5 (20%); Dukes' D, 0 of 4 (0%); for group C: Dukes' A, 2 of 31 (6%); Dukes' B, 6 of 32 (19%); Dukes' C, 16 of 44 (36%); Dukes' D, 0 of 8 (0%).

The actuarial probability of distant recurrence at 5 years was 23% in group A, 18% in group B, and 23% in group C. There was not a significant difference among groups A, B, and C. The distant recurrence rates by stage for group A were: Dukes' A, 1 of 32 (3%); Dukes' B, 3 of 16 (19%); Dukes' C, 17 of 41 (41%); for group B: Dukes' A, 0 of 7 (0%); Dukes' B, 0 of 3 (0%); Dukes' C, 1 of 5 (20%); and for group C: Dukes' A, 1 of 31 (3%); Dukes' B, 3 of 32 (9%); Dukes' C, 16 of 44 (36%).

The cumulative survival rate in each group is shown in Figure 6. Twenty-five patients in the radiation group (groups A and B) died of rectal cancer, 24 had persistent distant metastasis, and 1 had local recurrence. The actuarial probabilities of survival rate for 5 years were 62% in group A, 63% in group B, and 65% in group C. There were no significant differences among the groups for these parameters. The actual 5-year survival by Dukes' stage for group A was: Dukes' A 97%, Dukes' B 94%, Dukes' C 51%, Dukes' D 29%; for group B: Dukes' A 100%, Dukes' B 33%, Dukes' C 40%; Dukes' D 25%; and for group C: Dukes' A 100%, Dukes' B 78%, Dukes' C 50%; Dukes' D 13%.

DISCUSSION

Radiation therapy has been receiving increasing attention in the treatment of rectal carcinoma with curative intent [1,2]. Brachytherapy using endocavitary X-ray radiation for rectal carcinoma was introduced by Papillon et al. in 1951. Since they reported that endocavitary radiotherapy produced good local control, endocavitary irradiation has been more accepted by surgeons [11]. We use Cobalt-60 as the source of gamma-ray, which is mostly used as the pellet source of a remote afterloader in Japan. The advantage of contact radiation therapy such as IBT is that the dose of radiation falls off sharply around the radioactive sources, and the farther away the tissues are, the lower the dose received. The preoperative administration of IBT also has the advantage of not prolonging the interval from initial radiation to surgical operation. External beam radiation therapy at the total dose of 20–45 Gy takes 4 or 8 weeks to complete because of its multifractionation [1,12,13]. The preoperative IBT in our series, however, could administer a similar dose over a week, and the interval from initial radiation to operation could thus be shortened.

Doses of endocavitary radiation used have been as varied as 2,500–15,000 R [11] and 4,000–12,000 cGy [14]. Only a few studies describing complications after IBT have been reported [15]. However, the high-dose group (group B) had severe complications in the postoperative period. Many of the patients in group B suffered from high-frequency stooling and soiling in the early postoperative period, and urgency and incomplete evacuation in the late phase [10]. Pathological examination revealed no significant difference in the radiation effect between groups A and B. This result suggests that a moderate dose of IBT may be appropriate prior to surgery.

Various large series using external beam radiation elicited some discrepancy of prognostic result in radiotherapy combined with surgery for rectal carcinoma. The overall survival rate was reported as 60% by the Veterans Administration Surgical Adjuvant Group (VASAG) [12],

70% by the European Organization for Research and Treatment of Cancer (EORTC) [13], and 55% by the Medical Research Council (MRC) Working Party [16]. Although improvement of local control was obtained, adjuvant radiotherapy did not improve the overall survival rate in these series. Improvement of survival rate in the radiation group was demonstrated only under the limited condition as follows: the cases treated with APE in the VASAG trial and the cases treated with curative operation in the EORTC trial. These variations may be related to the type of operation and to the clinicopathologic stage in the multi-institutional trial. To our knowledge, there are no reports concerning long-term oncologic results of IBT combined radical surgery. Five-year survival rates after endocavitary radiation only were reported as 56% by Papillon [17] and as 90% in selected patients by Sischy [14]. In our series, the overall 5-year survival rates were similar among the three groups; group A, 62%; group B, 63%; group C, 65%. We found out that tumor size and viable tumor nest in the resected specimen of the IBT group (groups A and B) were smaller than those in the no radiation group (group C), and observed evidence of the IBT effect on involved lymph nodes. However, the incidence of Dukes' C tumors or the rate of distal recurrence was not significantly different among three groups.

Our consecutive series in a single institute could assure uniform surgical strategy and procedures during the trial, although our study was not randomized. The prevalence of SSR was 72% in group A, 63% in group B, and 42% in group C (group A vs. group C, $P < 0.0001$). The local recurrence rate was 11% in group A, 6% in group B, and 26% in group C. There was a significant difference between groups A and C in overall local failures ($P = 0.005$). This finding suggested that the improvement of local control by preoperative IBT might avoid conversion to a permanent stoma after SSR.

In conclusion, an improvement of local control was observed by an application of preoperative IBT after radical surgery. The option of IBT might be useful to allow performance of SSR for low rectal carcinoma which was usually treated by APE [18]. The moderate-dose IBT group had the same decreased cancer cells as the high-dose IBT group, with fewer postoperative complications. The findings from this series show that the use of preoperative IBT can contribute to a better outcome for rectal carcinoma.

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